Paper No. 42

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte CHARLES T. ESMON, NAOMI L. ESMON,
DEBORAH J. STEARNS and
SHINICHIRO KUROSAWA

Appeal No. 1997-0483
Application No. 07/648,900[1]

ON BRIEF

Before ROBINSON, SPIEGEL, and SCHEINER, Administrative Patent Judges.

SPIEGEL, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner finally rejecting claims 5, 6, 13, 16, 19, 21 and 22 and refusing to allow claim 20 as amended subsequent to the final rejection, which are all of the claims pending in this application.[2]

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[1] Application for patent filed January 31, 1991. According to appellants, this application is a continuation-in-part of application 07/214,774 filed July 5, 1988, now abandoned.

[2] Entry of the amendment filed May 13, 1996 (Paper No. 40) amending claim 20 was authorized by the examiner in the communication mailed June 11, 1996 (Paper No. 41). However, the amendment has not been physically entered. Therefore, upon return of the application to the jurisdiction of the examiner, this clerical oversight should be corrected.

Claims 5, 6, 13, 19 and 20 are illustrative and read as follows.

5. A polypeptide consisting essentially of an amino acid sequence which corresponds to residues 407 to 486 of a mammalian thrombomodulin as shown in Figure 6.[3]

6. The polypeptide of claim 5 having the formula:
Phe Cys Asn Gln Thr Ala Cys Pro Ala Asp Cys Asp Pro Asn Thr Gln
Ala Ser Cys Glu Cys Pro Glu Gly Tyr Ile Leu Asp Asp Gly Phe Ile
Cys Thr Asp Ile Asp Glu Cys Glu Asn Gly Gly Phe Cys Ser Gly Val
Cys His Asn Leu Pro Gly Thr Phe Glu Cys Ile Cys Gly Pro Asp Ser
Ala Leu Ala Arg His Ile Gly Thr Asp Cys Asp Ser Gly Lys Val Asp.

13. A pharmaceutical composition comprising an amount of the polypeptide of claim 5 effective to inhibit coagulation in a mammalian subject in need thereof and a pharmaceutically acceptable carrier.

19. A method for inhibiting coagulation in a mammalian subject in need thereof comprising administering to the subject an effective amount of an isolated polypeptide consisting essentially of an amino acid sequence which corresponds to residues 407 to 486 of a mammalian thrombomodulin as shown in Figure 6 in combination with a pharmaceutically acceptable carrier, to inhibit the clotting activity of thrombin without increasing protein C activation.

20. The polypeptide of claim 5 which is a portion of a thrombomodulin of an animal selected from the group consisting of human, rabbit, and bovine.

A reference relied on by the examiner is (answer, p. 7):

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[3] According to the specification (p. 3), "Figure 6 shows schematically the amino acid structure of human el-TM [i.e., active elastase proteolytic product of thrombomodulin (see specification, p. 10, Example 2)] which corresponds to residues 234 to 486 of thrombomodulin. The CNBr fragments, CB1, CB2 and CB3, begin at residues 234, 310 and 407, respectively."

Jackman et al. (Jackman), "Characterization of a thrombomodulin cDNA reveals structural similarity to the low density lipoprotein receptor," Proceedings of the National Academy of Sciences, USA, Vol. 83, pp. 8834-8838 (December 1986)

References relied on by the appellants are (brief, pp. 16-18):

Nagashima et al. (Nagashima), "Alanine-scanning Mutagenesis of the Epidermal Growth Factor-like Domains of Human Thrombomodulin Identifies Critical Residues for Its Cofactor Activity," The Journal of Biological Chemistry, Vol. 268, No. 4, pp. 2888-2892 (February 5, 1993)

Clarke et al. (Clarke), "The Short Loop between Epidermal Growth Factor-like Domains 4 and 5 Is Critical for Human Thrombomodulin Function," The Journal of Biological Chemistry, Vol. 268, No. 9, pp. 6309-6315 (March 25, 1993)

Zushi et al. (Zushi), "Aspartic Acid 349 in the Fourth Epidermal Growth Factor-like Structure of Human Thrombomodulin Plays a Role in Its Ca^{+2} -mediated Binding to Protein C," The Journal of Biological Chemistry, Vol. 266, No. 30, pp. 19886-19889 (October 25, 1991)

Hayashi et al. (Hayashi), "Further Localization of Binding Sites for Thrombin and Protein C in Human Thrombomodulin," The Journal of Biological Chemistry, Vol. 265, No. 33, pp. 20156-20159 (November 25, 1990)

ISSUES[4]

Claims 5, 6, 13, 16 and 19-22 stand rejected under 35 U.S.C. § 112, first and second paragraphs, as indefinite and non-enabled. We reverse.

In reaching our decision in this appeal we have given careful consideration to the appellants' specification and claims and to the respective positions articulated by the

[4] The "New ground of rejection" of claim 20 under 35 U.S.C. § 112, second paragraph, as indefinite (answer, pp. 7-8) was withdrawn by the examiner in view of the amendment to claim 20 filed May 13, 1996 (Paper No. 40) in the communication mailed June 11, 1996 (Paper No. 41).

appellants and the examiner. We make reference to the examiner's answer (Paper No. 37, mailed March 5, 1996) for the examiner's reasoning in support of the rejections and to the appellants' brief (Paper No. 36, filed November 13, 1995) and to appellants' reply brief (Paper No. 39, filed May 13, 1996) for the appellants' arguments thereagainst.

BACKGROUND

Thrombomodulin is an endothelial cell surface glycoprotein that forms a high affinity complex with thrombin wherein the clotting activity of thrombin is inhibited. Thrombomodulin is organized into five regions: (1) an amino terminal, hydrophobic region (residues 1-244); (2) a cysteine-rich region containing six repeated structures homologous to the epidermal growth factor precursor, called EGF-like or EGF-homology domains (residues 245-480); (3) a serine/threonine/proline-rich region with *O*-glycosylation sites (residues 481-514); (4) a hydrophobic transmembrane region (residues 515-537); and (5) a cytosolic tail (residues 538-575). As shown in Figure 6, the residues of the cysteine-rich region can be separated into three fragments by cyanogen bromide digestion, i.e., CB-1, CB-2 and CB-3, beginning at residues 234, 310 and 407, respectively. [Specification, p. 1, para. 3; p. 2, para. 2-3; p. 3, penultimate para.; Figure 6; p. 5, para. 2.]

The claimed invention is directed to polypeptides derived from thrombomodulin and their use in inhibiting coagulation (brief, p. 2, last para.).

OPINION

A. Claim interpretation

All of the appealed claims depend directly or indirectly on independent claim 5. Claim 5 recites a polypeptide consisting essentially of an amino acid sequence which corresponds to the residues 407 to 486 of a mammalian thrombomodulin as shown in Figure 6 (emphasis added).

During ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification. In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320,1322 (Fed. Cir. 1989). Unless otherwise defined by applicants in the specification, claim language should be read in light of the specification as it would be interpreted by those of ordinary skill in the art. In re Sneed, 710 F.2d 1544, 1548, 218 USPQ 385, 388 (Fed. Cir. 1983). Thus, our analysis begins with determining what is meant by the terms "corresponds to" and "consisting essentially of."

There is no evidence that appellants intended "corresponds to" to carry any extraordinary meaning. The first and second definitions for "correspond" in the American Heritage Dictionary, second college edition (1982) (copy attached), are

> 1. To be in agreement, harmony, or conformity; be consistent or compatible: ... 2. To be similar, parallel, equivalent, or equal in character, quantity, origin, structure, or function: ...

According to the specification, "polypeptides of this invention are not species specific," ... e.g., "a polypeptide having a structure identical to a functional fragment of rabbit thrombomodulin will be effective to bind human thrombin" (p. 9, para. 3). Example 13 compares the sequences of rabbit, human and bovine CB3, specifically identifying which residues are identical (p. 20). Figure 1 also compares the amino terminal sequences of rabbit, bovine and human CB3 fragments (see Example 3, pp. 10-11). In addition, the specification discloses that the invention include polypeptides which are not glycosylated (p. 25, para. 2) and polypeptides which have been altered at their termini to provide groups for cross-linking the polypeptide to the surface of an article (p. 8, para. 4 - p. 9, para. 2). Thus, referring to the specification, we interpret "corresponds to" consistent with its secondary dictionary definition, i.e., a "similar to."

In law, the "consisting essentially of" language renders the claims open for the inclusion of ingredients which do not materially affect the basic and novel characteristics of the claimed compositions. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1574, 224 USPQ 409, 411 (Fed. Cir. 1984); accord In re Herz, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). In re Janakirama-Rao, 317 F.2d 951, 954, 137 USPQ 893, 895-96 (CCPA 1963). The seminal issue is what are the basic and novel characteristics of residues 407 to 486 of a mammalian thrombomodulin as shown in Figure 6 the claimed invention, i.e., of CB3. According to the specification, the 80 residue

polypeptide of amino acid residues 407 to 486 binds thrombin, thereby inhibiting its clotting activity, without increasing protein C activation (see p. 4, penultimate para.; p. 6, para. 2; p. 7, para. 4; p. 9, para. 5; pp. 20--22, Examples 14-16; p. 25, para. 2).

Thus, we interpret the polypeptides of the claimed invention as encompassing polypeptides which identically correspond to residues 407 to 486 of a mammalian thrombomodulin as shown in Figure 6 as well as "similar" sequences having modifications both within the sequence, e.g., conservative substitutions at non-identical amino acid residues as suggested in specification Example 13, and additional substituents adjacent to the termini of the sequence, e.g., cross-linking groups suitable for attaching the polypeptide to a surface, and non-glycosylated derivatives thereof with the proviso that the sequence must be capable of binding to thrombin, thereby inhibiting its clotting activity, without affecting, i.e., increasing, protein C activation. We do not interpret claim 5 as reciting a polypeptide including additional amino acid residues up to and including residues 234 to 286, residues 310 to 486, or even the entire protein because such polypeptides significantly increase protein C activation (see e.g., specification, p. 4, para. 5).[5]

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[5] In the brief (pp. 18-19, § b.), appellants state:
The specification provides the amino acid sequences of thrombomodulin from several species and describes which regions, and residues within regions, are conserved. It is readily apparent to one skilled in the art that if the protein contains substitutions for an amino acid residue but is still biologically active, that the substituted amino acid is not essential for activity. Moreover, applicants have shown that not only are the claimed peptides active, but that longer fragments including other amino acids, up to and including

B. Rejection of claims 5, 6, 13, 16 and 19-22 under § 112, second paragraph

The legal standard for indefiniteness under 35 U.S.C. § 112, second paragraph, is whether a claim reasonably apprises those of skill in the art of its scope. In re Warmerdam, 33 F.3d 1354, 1361, 31 USPQ2d 1754, 1759 (Fed. Cir. 1994). "[D]efiniteness of the language employed must be analyzed --- not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." In re Moore, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971). According to the examiner, "claims 5 and 19 and those dependent therefrom (claims 6, 13, 16, and 20-22) are indefinite" in reciting the term "consisting essentially of" (answer, p. 3, last para.) because "it is unclear if this phrase includes variants of the recited sequence and if so what the scope of the variants included is" (answer, p. 8, para. 2, emphasis in the original). For reasons discussed supra, there has been no showing on this record by the examiner that one skilled in the art would have any particular difficulty in determining the meaning of "consisting essentially of" or of being reasonably apprised of the scope of the claims. Therefore, this rejection is reversed.

C. Rejection of claims 5, 13, 19, 21 and 22 under § 112, first paragraph, enablement[6]

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the entire protein, are biologically active.

[6] According to the examiner, the "first paragraph portion of the combined 35 U.S.C. § 112, first and second paragraph rejection does not apply to claims 6, 16 and 20" (answer, p. 1, § (1) Status of claims).

A specification complies with the enablement requirement of 35 U.S.C. § 112, first paragraph, if it allows one of ordinary skill in the art to make and use the claimed invention without undue experimentation and the examiner has the initial burden of establishing lack of enablement. In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

PPG. Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) (quotation and citation omitted); see also In re Wands, 858 F.2d 731, 736-40, 8 USPQ2d 1400, 1403-07 (Fed. Cir. 1988). The determination of what constitutes undue experimentation in a given case must be decided on the facts of each particular case and requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art.

According to the examiner,

> appellants have failed to enable the broad scope of the instant claims (except claims 6, 16 and 20 which are limited in scope to specific sequences) as the available sequence information of the three mammalian forms disclosed provides only very limited guidance with regard to what amino acid modifications could be predictably tolerated, e.g., such as substitution with those amino acids which differ (i.e., are not conserved) in particular positions between these mammal species or other conservative

> substitutions in these positions. However, since the positions which differ between species are few, it would require undue experimentation to determine what other substitutions in conserved positions can be made and the scope of the claims is not commensurate with the enablement .... [Answer, p. 4, para. 2.]

Here, the specification provides the CB3 amino acid sequences of thrombomodulin from several species, i.e., rabbit, bovine and human, and describes which residues within CB3 are conserved. The specification explicitly describes CB3 as being a cysteine-rich, EGF homology domain. Figure 6 illustrates the crosslink structure of EGFs 5 and 6, i.e., CB3. The basic and novel characteristics of the claimed invention are narrowly circumscribed to require the polypeptide be capable of binding thrombin so as to inhibit the clotting activity of thrombin without affecting, i.e., increasing, protein C activation. The specification provides specific guidance for determining whether a candidate polypeptide possesses such capability. Simply stating that it is possible to generate an enormous number of possible variants (answer, para. bridging pp. 12-13) does not establish that the experimentation is undue or that one of ordinary skill in the art would necessarily attempt every mathematically possible permutation of the residues shown to vary between rabbit, human and bovine CB3 without regard for the EGF-like nature of the polypeptide. The examiner has not explained why one skilled in the art would have had any particular difficulty in carrying out appellants' claimed invention without undue experimentation in view of this disclosure. Therefore, this rejection is reversed. Since the examiner has not

sustained her burden of establishing a prima facie case of nonenablement, we do not reach appellants' rebuttal evidence discussed on pages 16-18 of the brief.

. CONCLUSION

To summarize, the decision of the examiner to reject claims 5, 6, 13, 16 and 19-22 under 35 U.S.C. § 112, first and second paragraphs, as indefinite and non-enabled is reversed.

REVERSED

DOUGLAS W. ROBINSON Administrative Patent Judge	)
CAROL A. SPIEGEL Administrative Patent Judge	) BOARD OF PATENT) APPEALS) AND) INTERFERENCES
TONI R. SCHEINER Administrative Patent Judge	)

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APPEAL NO. 1997-0483 - JUDGE SPIEGEL
APPLICATION NO. 07/648,900

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APJ ROBINSON

DECISION: **REVERSED**

Prepared By:

DRAFT TYPED: 29 Jun 01

FINAL TYPED: